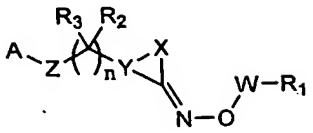
WE CLAIM

1. A compound of Formula I:



in which:

n is 0, 1 or 2;

R_1 is chosen from C_{6-10}aryl and C_{5-10}heteroaryl; wherein any aryl or heteroaryl of R_1 is optionally substituted by a radical chosen from C_{6-10}arylC_{0-4}alkyl, C_{5-6}heteroarylC_{0-4}alkyl, C_{3-8}cycloalkylC_{0-4}alkyl, C_{3-8}heterocycloalkylC_{0-4}alkyl or C_{1-10}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_1 can be optionally substituted by one to five radicals selected from the group consisting of halo, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy; and any alkyl group of R_1 can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, –$S(O)_2$–, –NR_4– and –O–; wherein R_4 is chosen from hydrogen or C_{1-6}alkyl;

R_2 and R_3 are independently chosen from hydrogen, C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkoxy, halo-substituted C_{1-6}alkyl and halo-substituted C_{1-6}alkoxy;

A is chosen from –$X_1C(O)OR_4$, –$X_1OP(O)(OR_4)_2$, –$X_1P(O)(OR_4)_2$, –$X_1P(O)OR_4$, –$X_1S(O)_2OR_4$, –$X_1P(O)(R_4)OR_4$ and 1*H*-tetrazol-5-yl; wherein X_1 is a bond or C_{1-6}alkylene and R_4 is chosen from hydrogen and C_{1-6}alkyl;

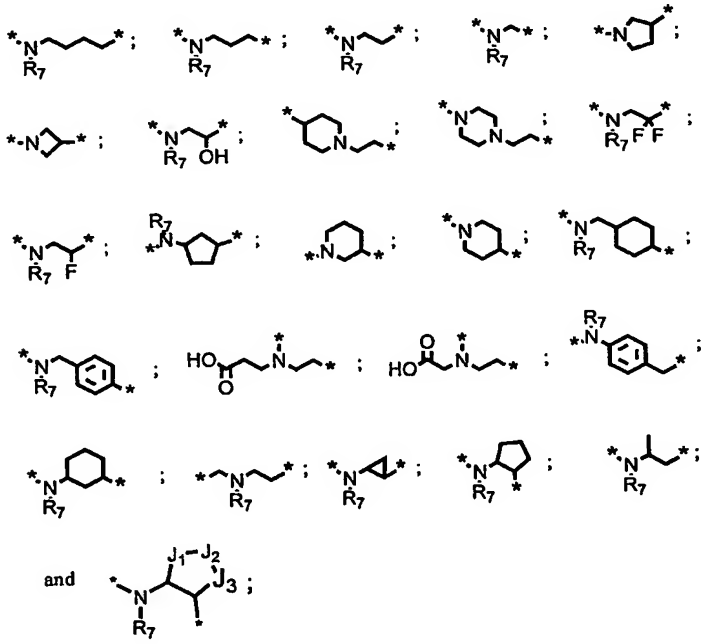
W is chosen from a bond, C_{1-6}alkylene and C_{2-6}alkenylene;

X is chosen from C_{2-4}alkylene and C_{2-4}alkenylene; wherein one methylene group of X can be replaced with an atom or group chosen from –O–, –S–, –S(O)–, –$S(O)_2$– and –NR_5–; wherein R_5 is hydrogen, C_{1-6}alkyl and –C(O)R_6; wherein R_6 is chosen from hydrogen and C_{1-6}alkyl; wherein any alkylene or alkenylene of X can further be substituted by 1 to 3 radicals selected from the group consisting of halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted C_{1-10}alkyl and halo-substituted C_{1-10}alkoxy;

Y is chosen from C_{6-10}aryl and C_{5-10}heteroaryl, wherein any aryl or heteroaryl of Y can be optionally substituted with 1 to 3 radicals chosen from halo, hydoxy, nitro, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted C_{1-10}alkyl and halo-substituted C_{1-10}alkoxy;

Z is C_{1-6}alkylene; wherein up to two methylene groups of Z can be replaced with divalent radicals chosen from $-NR_7-$, C_{3-8}cycloalkylene, C_{3-8}heterocycloalkylene and phenylene; wherein R_7 is chosen from hydrogen, C_{1-6}alkyl and $(CH_2)_{1-2}COOH$; wherein Z may further be substituted by 1 to 3 radicals chosen from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substitued-C_{1-6}alkyl and halo-substitued-C_{1-6}alkoxy; or when a $-NR_7-$ replaces at least one methylene group of Z, R_7 and Y together with the nitrogen atom to which R_7 is attached, forms C_{8-14}heteroarylene; and the pharmaceutically acceptable salts, hydrates, solvates, isomers and prodrugs thereof.

2. The compound of claim 1 in which n is 0 or 1 and Z is chosen from:



wherein the left and right asterisks of Z indicate the point of attachment between the $-[C(R_2)(R_3)]_n-$ group and A of Formula I, respectively; R_7 is chosen from hydrogen and C_{1-6}alkyl; and J_1, J_2 and J_3 are independently methylene or a heteroatom selected from the group

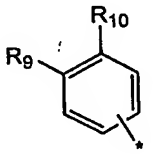
consisting of S, O and NR_4; wherein R_4 is hydrogen or C_{1-6}alkyl; with the proviso that the number of heteroatoms are 2 or less.

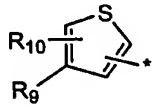
3. The compound of claim 1 in which R_1 is chosen from phenyl, naphthyl and thiophenyl optionally substituted by $C_{6-10}arylC_{0-4}alkyl$, $C_{5-6}heteroarylC_{0-4}alkyl$, $C_{3-8}cycloalkylC_{0-4}alkyl$, $C_{3-8}heterocycloalkylC_{0-4}alkyl$ or C_{1-10}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_1 can be optionally substituted by 1 to 5 radicals chosen from halo, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy; and any alkyl group of R_1 can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, $–S(O)_2–$, $–NR_4–$ and –O–; wherein R_4 is hydrogen or C_{1-6}alkyl.

4. The compound of claim 1 in which Y is chosen from phenyl, pyridine, pyrimidine, thiophene, furan, thiazole and oxazole; each of which can be optionally substituted with 1 to 3 radicals chosen from halo, hydoxy, nitro, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted C_{1-10}alkyl and halo-substituted C_{1-10}alkoxy.

5. The compound of claim 1 in which R_2 and R_3 are both hydrogen and A is chosen from $–C(O)OR_4$ and 1*H*-tetrazol-5-yl; wherein R_4 is chosen from hydrogen and C_{1-6}alkyl.

6. The compound of claim 1 in which R_1 is chosen from:



and


;

wherein the asterisk is the point of attachment of R_1 with W; R_9 is $C_{6-10}arylC_{0-4}alkyl$, $C_{5-6}heteroarylC_{0-4}alkyl$, $C_{3-8}cycloalkylC_{0-4}alkyl$, $C_{3-8}heterocycloalkylC_{0-4}alkyl$ or C_{1-10}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_9 can be optionally substituted by 1 to 3 radicals chosen from halo, C_{1-10}alkyl, C_{1-10}alkoxy, halo-

substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy; and any alkyl group of R_9 can optionally have a methylene replaced by an atom or group chosen from –S–, –S(O)–, –$S(O)_2$–, –NR_4– and –O–; wherein R_4 is hydrogen or C_{1-6}alkyl; and R_{10} is selected from halo, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy.

7. The compound of claim 1 chosen from: 3-{[5-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl]-amino}-propionic acid; 1-[5-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl]-azetidine-3-carboxylic acid; 3-{[6-chloro-4-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-chroman-7-ylmethyl]-amino}-propionic acid; 3-{[3-chloro-5-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl]-amino}-propionic acid; 1-[3-Chloro-5-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl]-azetidine-3-carboxylic acid; 1-[5-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-3-methoxy-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl]-azetidine-3-carboxylic acid; 3-{[5-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-3-methoxy-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl]-amino}-propionic acid; 3-{[8-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-5,6,7,8-tetrahydro-quinolin-3-ylmethyl]-amino}-propionic acid; 1-[8-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-5,6,7,8-tetrahydro-quinolin-3-ylmethyl]-azetidine-3-carboxylic acid; 3-{4-[5-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-5,6,7,8-tetrahydro-naphthalen-2-yl]-piperazin-1-yl}-propionic acid; 3-{[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-indan-5-ylmethyl]-amino}-propionic acid; 1-[8-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl]-azetidine-3-carboxylic acid; 3-{[8-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl]-amino}-propionic acid; 3-{[5-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-3-ethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethyl]-amino}-propionic acid; 3-{[4-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-chroman-6-ylmethyl]-amino}-propionic acid; 3-{[4-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-chroman-7-ylmethyl]-amino}-propionic acid; 1-[4-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-chroman-7-ylmethyl]-azetidine-3-carboxylic acid; 3-{[4-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-3,4-dihydro-2H-pyrano[2,3-b]pyridin-7-ylmethyl]-amino}-propionic acid; 1-[4-(4-cyclohexyl-3-

trifluoromethyl-benzyloxyimino)-3,4-dihydro-2H-pyrano[2,3-b]pyridin-7-ylmethyl]-azetidine-3-carboxylic acid; 1-[4-(4-cyclohexyl-3-methyl-benzyloxyimino)-chroman-7-ylmethyl]-azetidine-3-carboxylic acid; and 3-{[4-(4-cyclohexyl-3-methyl-benzyloxyimino)-chroman-7-ylmethyl]-amino}-propionic acid.

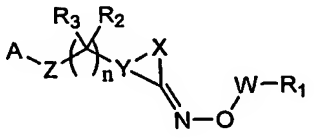
8. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.

9. A method for treating a disease in an animal in which alteration of EDG/S1P receptor mediated signal transduction can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease, which method comprises administering to the animal a therapeutically effective amount of a compound of Claim 1.

10. A method for preventing or treating disorders or diseases mediated by lymphocytes, for treating acute or chronic transplant rejection or T-cell mediated inflammatory or autoimmune diseases, for inhibiting or controlling deregulated angiogenesis, or for treating diseases mediated by a neo-angiogenesis process or associated with deregulated angiogenesis in a subject comprising administering to the subject in need thereof an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

11. The use of a compound of claim 1 in the manufacture of a medicament for treating a disease in an animal in which alteration of EDG/S1P receptor mediated signal transduction contributes to the pathology and/or symptomology of the disease.

12. A process for preparing a compound of Formula I:



in which:

n is 0, 1 or 2;

R_1 is chosen from C_{6-10}aryl and C_{5-10}heteroaryl; wherein any aryl or heteroaryl of R_1 is optionally substituted by a radical chosen from C_{6-10}arylC_{0-4}alkyl, C_{5-6}heteroarylC_{0-4}alkyl, C_{3-8}cycloalkylC_{0-4}alkyl, C_{3-8}heterocycloalkylC_{0-4}alkyl or C_{1-10}alkyl; wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl group of R_1 can be optionally substituted by one to five radicals selected from the group consisting of halo, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted-C_{1-10}alkyl and halo-substituted-C_{1-10}alkoxy; and any alkyl group of R_1 can optionally have a methylene replaced by a member of the group consisting of –S–, –S(O)–, –$S(O)_2$–, –NR_4– and –O–; wherein R_4 is chosen from hydrogen or C_{1-6}alkyl;

R_2 and R_3 are independently chosen from hydrogen, C_{1-6}alkyl, halo, hydroxy, C_{1-6}alkoxy, halo-substituted C_{1-6}alkyl and halo-substituted C_{1-6}alkoxy;

A is chosen from $–X_1C(O)OR_4$, $–X_1OP(O)(OR_4)_2$, $–X_1P(O)(OR_4)_2$, $–X_1P(O)OR_4$, $–X_1S(O)_2OR_4$, $–X_1P(O)(R_4)OR_4$ and 1*H*-tetrazol-5-yl; wherein X_1 is a bond or C_{1-6}alkylene and R_4 is chosen from hydrogen and C_{1-6}alkyl;

W is chosen from a bond, C_{1-6}alkylene and C_{2-6}alkenylene;

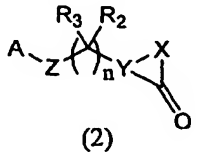
X is chosen from C_{2-4}alkylene and C_{2-4}alkenylene; wherein one methylene group of X can be replaced with an atom or group chosen from –O–, –S–, –S(O)–, –$S(O)_2$– and –NR_5–; wherein R_5 is hydrogen, C_{1-6}alkyl and –$C(O)R_6$; wherein R_6 is chosen from hydrogen and C_{1-6}alkyl; wherein any alkylene or alkenylene of X can further be substituted by 1 to 3 radicals selected from the group consisting of halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted C_{1-10}alkyl and halo-substituted C_{1-10}alkoxy;

Y is chosen from C_{6-10}aryl and C_{5-10}heteroaryl, wherein any aryl or heteroaryl of Y can be optionally substituted with 1 to 3 radicals chosen from halo, hydoxy, nitro, C_{1-10}alkyl, C_{1-10}alkoxy, halo-substituted C_{1-10}alkyl and halo-substituted C_{1-10}alkoxy;

Z is C_{1-6}alkylene; wherein up to two methylene groups of Z can be replaced with divalent radicals chosen from –NR_7–. C_{3-8}cycloalkylene, C_{3-8}heterocycloalkylene and phenylene; wherein R_7 is chosen from hydrogen, C_{1-6}alkyl and $(CH_2)_{1-2}COOH$; wherein Z may further be substituted by 1 to 3 radicals chosen from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substitued-C_{1-6}alkyl and halo-substitued-C_{1-6}alkoxy; or when a –NR_7– replaces

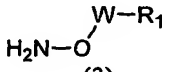
at least one methylene group of Z, R_7 and Y together with the nitrogen atom to which R_7 is attached, forms C_{8-14}heteroarylene; which process comprises:

(a) reacting a compound of formula 2:



(2)

with a compound of formula 3:



(3)

in which A, W, X, Y, Z, R_1, R_2, R_3 and n are as defined for Formula I above; and

(b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;

(c) optionally converting a salt form of a compound of the invention to a non-salt form;

(d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;

(e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;

(f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

(g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and

(h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.